DATA EVALUATION REPORT 012237

XDE-105 (SPINOSAD)

Study Type: 83-1b; 12-Month Oral Chronic Toxicity Study in Dogs

Work Assignment No. 1-22B (MRID 43701504)

Prepared for

Health Effects Division
Office of Pesticide Programs
U.S. Environmental Protection Agency
1921 Jefferson Davis Highway
Arlington, VA 22202

Prepared by

Pesticides Health Effects Group
Sciences Division
Dynamac Corporation
2275 Research Boulevard
Rockville, MD 20850-3268

Primary Reviewer:
Kathleen Ferguson, Ph.D

Signature: Kathleen Patten Ferguson
Date: 2-28-96

Secondary Reviewer:
William McLellan, Ph.D.

Signature:
Date:

Project Manager:
William J. Spangler, Ph.D.

Signature: William J. Spangler
Date: 2/28/96

Quality Assurance:
Reto Engler, Ph.D.

Signature: Reto Engler by WJS
Date: 2/28/96

Disclaimer

This Data Evaluation Report may have been altered by the Health Effects Division subsequent to signing by Dynamac Corporation personnel.

EPA Reviewer: R.L. Gardner, ~~Ph.D.~~ Roger Gardner, Date 4-2-97
Review Section I, Toxicology Branch I (7509C)
EPA Secondary Reviewer: M. Copley, D.V.M., D.A.B.T. MC, Date 5/27/97
Review Section I, Toxicology Branch I (7509C)

DATA EVALUATION RECORD

STUDY TYPE: Chronic Oral Toxicity [feeding] - dogs
OPPTS Number: 870.4100 OPP Guideline Number: §83-1b

DP BARCODE: D219011 SUBMISSION CODE: S492760
P.C. CODE: 110003 TOX. CHEM. NO.: None

TEST MATERIAL (PURITY): XDE-105 (87.2% ai)

SYNONYMS: Spinosad

CITATION: Harada, T. (1995) XDE-105: 12-Month Oral Chronic Toxicity Study in Dogs. The Institute of Environmental Toxicology, 2-772, Suzuki-cho, Kodaira-shi, Tokyo 187, Japan. Laboratory Project Study ID IET 91-0080. January 30, 1995. MRID 43701504. Unpublished.

SPONSOR: DowElanco Division, Dow Chemical Japan Ltd, Tennoz Central Tower, 2-24, Higashi Shinagawa 2-chome, Shinagawa-ku, Tokyo 140, Japan.

EXECUTIVE SUMMARY:

In a chronic toxicity study (MRID 43701504), XDE-105 (Spinosad, 87.2% ai) was administered to four beagle dogs/sex/dose in the diet at dose levels of 50/60, 100/120, or 300/360 ppm (1.44, 2.68, or 8.46 mg/kg/day, respectively, for males; 1.33, 2.72, or 8.22 mg/kg/day, respectively, for females) for 52 weeks.

Male beagles in the 300/360 ppm treatment group had serum levels of alanine aminotransferase 257 and 207% higher at 26 and 52 weeks, respectively; and serum levels of aspartate aminotransferase and triglycerides 147 and 132% higher, respectively, at 26 weeks than beagles in the control group; no comparable differences were observed in females in the 300/360 ppm group. Male and female beagles in the 300/360 ppm treatment groups were found to have slight vacuolated cell aggregations in lymphoid tissues (4/4 males, 2/4 females), slight to moderate inflammation of arteries in the epididymis (1/4 males) or cerebral meninges (1/4 females), and slight glandular cell vacuolation of the parathyroid (2/4 males). Although female beagles in the 300/360 ppm treatment group had absolute and relative thyroid weights that were approximately 160% higher than beagles in the control and lower dose treatment groups, no treatment-related microscopic changes were observed in these tissues. No dogs died during the study. No treatment-related

differences were observed between the clinical appearance, body weights, food consumption, ophthalmology, hematology, or urine of the treated and control animals. No definitive treatment-related differences in organ weights were observed between the treated and control animals. No gross pathological differences were observed between beagles in the treatment and control groups. All microscopic tissue abnormalities, other than those mentioned, occurred randomly and sporadically in all study groups. No neoplastic tissue was observed in beagles in the treatment or control groups. **The LOEL is 8.22 mg/kg/day (300/360 ppm), based on increases in serum alanine aminotransferase, aspartate aminotransferase, and triglycerides levels, and the presence of tissue abnormalities, including vacuolated cell aggregations, arteritis, and glandular cell vacuolation (parathyroid). The NOEL is 2.68 mg/kg/day (100/120 ppm).**

This chronic toxicity study in dogs is **acceptable** and does satisfy the guideline requirement for a chronic oral toxicity study (§83-1b) in dogs.

COMPLIANCE: Signed and dated GLP, Data Confidentiality, Quality Assurance, and Flagging statements were provided.

I. MATERIALS AND METHODS

A. MATERIALS

1. Test Material: XDE-105
   Description: Off-white to pale yellow powder
   Lot/Batch #: AGR293707
   Purity: 87.2% ai
   Stability of compound: Stable at room temperature
   CAS #: Not provided
   Structure: Not provided

2. Vehicle and/or positive control: None

3. Test animals: Species: Beagles
   Strain: Not identified
   Age and weight at study initiation: 6-7 months of age; body weights 7.5-9.2 kg for males, 8.1-10.0 kg for females
   Source: Ohito Biotec Center Inc., Shuzenji-cho, Tagata-gun, Shizuoka
   Housing: Individual stainless steel cages (835 x 900 x 800 mm) within a dog room
   Diet: powder certified DS diet, ad libitum (but restricted to 300 g/dog/day prior to 13 weeks and to 250 g/dog/day after 13 weeks)
   Water: sterilized well water, ad libitum
   Environmental conditions:
   Temperature: 24 ± 2 C

Humidity: 55 ± 10%
Air changes: 15 per hour
Photoperiod: 12-hour light/12-hour dark
Acclimation period: 3-4 weeks

B. STUDY DESIGN

1. In life dates Start: 11/25/92 End: 12/24/93

2. Animal assignment

Dogs (16 of each sex) were assigned to the test groups in Table 1 on the basis of body weight using a computer-assisted randomization procedure.

TABLE 1. STUDY DESIGN

Test Group	Conc. in Diet* (ppm)	Nominal Dose to Animal (mg/kg/day)	Animals Assigned	
			Male	Female
Control	0	0	4	4
Low	50/60	1.5	4	4
Mid	100/120	3.0	4	4
High	300/360	9.0	4	4

* To prevent obesity, the amount of food provided the dogs each day was reduce at 13 weeks. To maintain the same level of treatment, the concentration of XDE-105 in the feed was increased accordingly.

3. Dose selection rationale

Dose selection was based on the results of a 13-week subchronic study with dogs (MRID 43444102; reviewed by EPA in a report dated 5/30/95) in which XDE-105 concentrations of 150, 300, and 900 (females) or 1350/900 (males) ppm were evaluated. The study author concluded that the NOEL was 150 ppm. The LOEL was 300 ppm, based on the observance of cytoplasmic vacuolation or vacuolated cell aggregation in a variety of tissues.

4. Diet preparation and analysis

The treated diet was prepared prior to the initiation of the study and every 4 weeks thereafter. Appropriate amounts of

test substance were mixed with a portion of the basal feed using a mortar, then the mixture was blended with additional feed using a mechanical mixer. The treated feed was stored in sealed plastic bags within a plastic container in the dark at 4 C. Approximately once each week, a portion of the treated feed was removed to the animal room and stored in an aluminum container at room temperature until moistened (to minimize spillage) and fed to the animals. Uneaten feed was removed and replaced daily.

To determine the stability of XDE-105 in the feed, samples were collected from the 50 ppm treatment feed that was prepared immediately prior to the initiation of feeding. The samples were stored moist at room temperature for 24 hours; dry at room temperature for 0, 5, or 8 days; or dry at 4 C in the dark for 5 weeks. To determine the homogeneity of the XDE-105/feed mixture, samples were collected from the top, middle, and bottom portions of the treated feed that was prepared immediately prior to the initiation of feeding. To confirm the concentration of XDE-105 in the treated feed, samples of the feed for each dose level were collected at each preparation interval from the middle of the mixer. The control diet was also analyzed to confirm that contamination had not occurred.

Results:

Stability Analysis (duplicate samples):
0 day (initial sample)- 48.0 ppm, 48.1 ppm
Room temperature, moistened 50 ppm
1 day - 45.4 ppm, 46.2 ppm
Room temperature, dry 50 ppm
5 days - 46.3 ppm, 46.8 ppm
8 days - 43.7 ppm, 45.8 ppm
4 C, dry 50 ppm
35 days - 46.6 ppm, 47.1 ppm
Homogeneity Analysis:
50 ppm: 46.5-49.6 ppm (average 48.0 ppm, 96% nominal)
100 ppm: 94.6-105.1 ppm (average 99.3 ppm, 99% nominal)
300 ppm: 283.5-291.7 ppm (288 ppm; 96% nominal)
Concentration Analysis (Appendix 1):
50 ppm treatment: 46.0-52.9 ppm
60 ppm treatment: 52.8-59.9 ppm
100 ppm treatment: 91.7-105.9 ppm
120 ppm treatment: 109.1-120.9 ppm
300 ppm treatment: 283.5-306.1 ppm
360 ppm treatment: 315.1-376.2 ppm

The analytical data indicated that the mixing procedure was adequate and that the variance between nominal and actual dosage to the animals was acceptable.

5. Statistics

Body weights, urine volume and specific gravity, hematology, blood biochemistry, and organ weights were analyzed using either Dunnett's or Scheffe's multiple comparison methods. Food consumption and all other urine parameters were analyzed using Mann-Whitney's U test. Clinical signs, mortality, ophthalmology, and pathology were analyzed using Fisher's exact probability test. Significance was determined at the 5 and 1% levels.

C. METHODS:

1. Observations

Animals were inspected at least once a day for signs of toxicity and mortality. Each animal was given a detailed physical examination weekly, and a detailed neurologic examination during weeks 49-50.

2. Body weight

Animals were weighed at the initiation of treatment, once each week through 13 weeks, and once every 4 weeks thereafter. Animals were also weighed before necropsy.

3. Food consumption and compound intake

Food consumption for each animal was determined daily during the dosing period. Mean daily diet consumption was calculated as g food/animal/day. Compound intake was calculated as mg food/kg body weight/day.

4. Ophthalmoscopic examination

Ophthalmoscopic exams were performed on all dogs using a direct ophthalmoscope and a portable fundus camera prior to study initiation and during weeks 26 and 52 of dosing.

5. Blood

Blood was collected prior to study initiation and during weeks 13, 26, and 52 of dosing. Samples were collected from the cephalic vein of all animals following overnight starvation. Hematology analyses were conducted on all samples; clinical chemistry analyses were conducted on all samples except those collected during week 13. The CHECKED (X) parameters were examined.

a. Hematology

X	Hematocrit (HCT)*	X	Leukocyte differential count*
X	Hemoglobin (HGB)*	X	Mean corpuscular HGB (MCH)
X	Leukocyte count (WBC)*	X	Mean corpusc. HGB conc.(MCHC)
X	Erythrocyte count (RBC)*	X	Mean corpusc. volume (MCV)
X	Platelet count*		Reticulocyte count
	Blood clotting measurements*		
	(Thromboplastin time)		
	(Clotting time)		
	(Prothrombin time)		

* Required for chronic studies based on Subdivision F Guidelines.

b. Clinical Chemistry

	ELECTROLYTES		OTHER
X	Calcium*	X	Albumin*
X	Chloride*	X	Blood creatinine*
	Magnesium	X	Blood urea nitrogen*
X	Phosphorus*	X	Total Cholesterol
X	Potassium*	X	Globulins
X	Sodium*	X	Glucose*
		X	Total bilirubin
		X	Total serum protein (TP)*
	ENZYMES	X	Triglycerides
			Serum protein electrophores
X	Alkaline phosphatase (ALK)	X	Albumin/globulin ratio
	Cholinesterase (ChE)		
X	Creatine phosphokinase		
	Lactic acid dehydrogenase (LDH)		
X	Serum alanine aminotransferase (also ALT, SGPT)*		
X	Serum aspartate aminotransferase (also AST, SGOT)*		
X	Gamma glutamyl transferase (also GGT, GGPT)		
	Glutamate dehydrogenase		

* Required for chronic studies based on Subdivision F Guidelines.

6. Urinalysis

Urine was collected from each animal (24-hour pooled sample) prior to study initiation and during weeks 13, 26, and 52 of dosing. The CHECKED (X) parameters were examined.

X	Appearance	X	Glucose
X	Volume	X	Ketones
X	Specific gravity	X	Bilirubin
X	pH	X	Blood
X	Sediment (microscopic)		Nitrate
X	Protein	X	Urobilinogen

7. Sacrifice and Pathology

All animals that died and that were sacrificed on schedule were subject to gross pathological examination and the CHECKED (X) tissues were collected for histological examination. The (XX) organs, in addition, were weighed.

	DIGESTIVE SYSTEM		CARDIOVASC./HEMAT.		NEUROLOGIC
X	Tongue	X	Aorta*	XX	Brain*
X	Buccal mucosa	XX	Heart*	X	Periph.nerve*
X	Tonsils	X	Bone marrow*	X	Spinal cord (3 levels)*T
X	Salivary glands*	X	Lymph nodes*		
X	Esophagus*	XX	Spleen*	XX	Pituitary*
X	Stomach*	X	Thymus*	X	Eyes (optic n.)*T
X	Duodenum*				
X	Jejunum*		UROGENITAL		GLANDULAR
X	Ileum*				
X	Cecum*	XX	Kidneys*+	XX	Adrenal gland*
X	Colon*	X	Urinary bladder*	X	Lacrimal gland[T]
X	Rectum*	XX	Testes*+	X	Mammary gland[T]
XX	Liver*+	X	Epididymides	XX	Parathyroids*++
X	Gall bladder*	X	Prostate	XX	Thyroids*++
XX	Pancreas*		Seminal vesicle		
		XX	Ovaries*+		
	RESPIRATORY	X	Uterus*		
		X	Penis		
X	Trachea*				
X	Lung*				
X	Nose (Nasal Cavity)				OTHER
X	Pharynx			X	Bone*
X	Larynx			X	Skeletal muscle*
				X	Skin*
				X	All gross lesions and masses*

* Required for chronic studies based on Subdivision F Guidelines
+ Organ weight required in chronic studies.
++ Organ weight required for non-rodent studies.
T = required only when toxicity or target organ

II. RESULTS

A. Observations

1. Mortality - No animals died during the course of the study.

2. Clinical Signs - No treatment-related differences were observed between the appearance of animals in the treatment and control groups. Epileptic convulsions were observed in two males, one in the control group and one in the 300/360 ppm group, that were littermates. One female in the control group exhibited decreased spontaneous motor activity and a bloody mucoid stool during weeks 13-14 of the study.

B. Body weight and weight gain

No treatment-related differences were observed between the body weights of the control and treated beagles during the study (Table 2). Body weights of the male beagles in the 50/60 ppm treatment group were lower than the control animals beginning about week 24, and gained statistical significance ($p < 0.05$) between 36 and 52 weeks; the weight of the four dogs in this group ranged from 10.0 to 11.2 kg (average 10.6 kg), compared to 10.3 to 12.7 kg for dogs in all other groups.

TABLE 2. AVERAGE BODY WEIGHTS AND BODY WEIGHT GAINS OF BEAGLES[a]

Conc. in Diet (ppm)	Body Weight (kg)				Total Body Weight Gain (kg)
	0 Weeks	13 Weeks	28 Weeks	52 Weeks	
Male					
0	8.6	11.4	11.7	12.3	3.7
50/60	8.6	10.8	10.5	10.6*	2.0
100/120	8.6	11.3	11.5	11.9	3.3
300/360	8.6	10.4	10.7	11.3	2.7
Female					
0	9.0	10.8	11.2	11.5	2.5
50/60	9.0	11.0	11.5	12.4	3.4
100/120	9.0	11.0	11.1	11.6	2.6
300/360	9.0	10.9	11.1	11.6	2.6

[a] Data obtained from Tables 5 and 6, pages 54-55, and Appendices 6 and 7, pages 154-157, in the study report. Body weight gains calculated by reviewer from average group weights at 0 and 52 weeks.
* Significantly different ($p < 0.05$) from the control.

C. Food consumption and compound intake

1. Food consumption - Food consumption by the treated animals was similar to pretest values and/or the control group throughout the study. In general, all animals ate all of the food that they were provided each day.

2. Compound consumption - During the study, male and female beagles ingested 89-96% of the nominal dose (Table 3).

TABLE 3: CONSUMPTION OF XDE-105[a]

Conc. in Diet (ppm)	Nominal Dose to Animal (mg/kg/day)	Consumption of Test Substance (mg/kg/day)	
		Male	Female
50/60	1.5	1.44	1.33
100/120	3.0	2.68	2.72
300/360	9.0	8.46	8.22

[a] Data obtained from Tables 9 and 10, pages 58-59, in the study report.

D. Ophthalmoscopic examination

No treatment-related abnormalities of the eyes were noted during the study.

E. Blood work

1. Hematology - No treatment-related differences in hematology were observed between the treated and control beagles. At the 26-week interval, male beagles in all treatment groups had eosinophil counts of 0.1-0.2 x $10^3/mm^3$, compared to 0.5 x $10^3/mm^3$ for the controls; and female beagles in the 300/360 ppm treatment group had erythrocyte counts of 7.35 x $10^6/mm^3$, compared to counts of 6.60-6.82 x $10^6/mm^3$ for female beagles in the control and lower treatment groups. Although the 26-week differences were statistically significant, the values were within the normal ranges for these parameters.

2. Clinical chemistry - Male beagles in the 300/360 ppm treatment group had higher mean serum levels of alanine aminotransferase (glutamic pyruvic transaminase, GPT) at 26 and 52 weeks, and higher serum levels of aspartate aminotransferase (glutamic oxaloacetic transaminase, GOT) and triglycerides (TG) at 26 weeks than beagles in the control and lower dose treatment groups (Table 4). The increases were transient and were not observed at 52 weeks. No other treatment-related differences in blood chemistry were observed between the 300/360 treatment and control male beagles, and no differences were observed between the 50/60 or 100/120 treatment beagles and the control male beagles

during the study.

No treatment-related differences in blood chemistry were observed between the treated and control female beagles during the study. One female in the control group (animal 101) had an elevated level of plasma alkaline phosphatase (ALP) activity at 13 weeks only; alkaline phosphatase activity for this dog was 111, 346, 166, and 67 U/L at pretest, 13, 26, and 52 weeks, respectively.

TABLE 4. ALANINE AMINOTRANSFERASE (GPT), ASPARTATE AMINOTRANSFERASE (GOT), AND TRIGLYCERIDES IN CONTROL AND HIGH-DOSE (300/360 PPM) MALE BEAGLES.[a]

Treatment Interval (weeks)	GPT (U/L)	GOT (U/L)	Triglycerides (mg/dL)
0 ppm Males			
0	40	32	37
26	44	34	41
52	40	32	42
300/360 ppm Males			
0	47	32	39
26	113	50*	54*
52	83	35	39

[a] Data obtained from Table 17, pages 94-99, in the study report.
* Significantly different ($p < 0.05$) from the control.

F. Urinalysis

No treatment-related differences in urinalysis parameters were observed between the treated and control beagles during the study.

G. Sacrifice and Pathology

1. Organ weight - Female beagles in the 300/360 ppm treatment group had absolute and relative thyroid weights that were

higher than beagles in the control and lower dose treatment groups (Table 5). No other treatment-related differences in organ weights were observed between the 300/360 treatment and control female beagles, and no differences were observed between the 50/60 or 100/120 treatment beagles and the control female beagles during the study. No significant differences in absolute or relative organ weights were observed between male beagles in the treatment and control groups.

TABLE 5. ABSOLUTE AND RELATIVE THYROID WEIGHTS OF FEMALE BEAGLES AFTER 52 WEEKS OF TREATMENT.[a]

Dose Level (ppm)	Thyroid Weight	
	Absolute (mg)	Relative
0	1043	0.0092
50/60	1069	0.0088
100/120	1024	0.0088
300/360	1662*	0.0143*

[a] Data obtained from Table 22, page 110-111, in the study report.
* Significantly different ($p < 0.05$) from the control.

2. Gross pathology - No pathological differences were observed between beagles in the treatment and control groups. Lesions, tissue discoloration, and other abnormalities occurred randomly and sporadically in all study groups.

3. Microscopic pathology

a) Non-neoplastic - Tissue abnormalities, including slight vacuolated cell aggregations in lymphoid tissues, slight to moderate inflammation of arteries in the epididymis or cerebral meninges, and slight glandular cell vacuolation of the parathyroid (males only), were observed in male and female beagles in the 300/360 ppm treatment group (Table 6). Mineralization of the kidneys (papillary) was seen in most dogs of both sexes in the control and treatment groups at terminal sacrifice. All other abnormalities occurred randomly and sporadically in all study groups.

TABLE 6. TREATMENT-RELATED ABNORMALITIES OBSERVED IN MALE AND FEMALE BEAGLES RECEIVING 300/360 PPM.[a]

Tissue Abnormalities	Number of Affected Animals/Total	
	Male	Female
Vacuolated cell aggregates:		
Spleen	1/4	1/4
Faucial tonsil	4/4	2/4
Lymph node	2/4	2/4
Intestine	3/4	0/4
Arteritis:		
Epididymis	1/4	0/4
Cerebral meninges	0/4	1/4
Glandular cell vacuolation:		
Parathyroid	2/4	0/4

[a] Data obtained from Tables 23 and 24, pages 112-118, and Appendices 20 and 21, pages 223-229, in the study report.

b) Neoplastic - No neoplastic tissue was observed in beagles in the treatment or control groups.

III. DISCUSSION

A. Investigator's Conclusions

The study author concluded that the LOEL for both sexes was 300/360 ppm, on the basis of changes in the blood chemistry indicative of hepatotoxicity and tissue abnormalities. The NOEL was 100/120 ppm.

B. Reviewer's Discussion

Although the rationale for dose selection appears adequate, the dogs may have been able to tolerate a slightly higher dose. XDE-105 had no apparent effect on male and female beagles in the 50/60 ppm or 100/120 ppm treatment groups

(1.44 or 2.68 mg/kg/day, respectively, for males; 1.33 or 2.72 mg/kg/day, respectively, for females) and only minimal toxic effects at the highest treatment level, 300/360 ppm (8.46 and 8.22 mg/kg/day for males and females, respectively). The effect of XDE-105 on beagles at 300/360 ppm included changes in blood chemistry (GOT/GPT) that suggested hepatotoxicity, but there were no liver weight changes or correlating histologic changes. Changes in the histology of other organs, including the spleen, faucial tonsil, lymph nodes, intestine, and parathyroid were observed.

No dogs died during the study. No treatment-related differences were observed between the clinical appearance, body weights, food consumption, ophthalmology, hematology, or urine of the treated and control animals.

Male beagles in the 300/360 ppm treatment group had serum levels of alanine aminotransferase 257 and 207% higher at 26 and 52 weeks, respectively; and serum levels of aspartate aminotransferase and triglycerides 147 and 132% higher, respectively, at 26 weeks than beagles in the control group; no comparable differences were observed in females in the 300/360 ppm group. Alanine aminotransferase, aspartate aminotransferase, and triglyceride levels in female beagles in the 300/360 ppm treatment group were not significantly different than beagles in the control and other treatment groups. No other differences in blood chemistry between the treated and control animals were noted.

Three of four female beagles in the 300/360 ppm treatment group had absolute thyroid weights of 1617-2146 mg and relative thyroid weights of 0.0151-0.0170, compared to absolute weights of 791-1435 mg and relative weights of 0.0060-0.0121 for beagles in the control and lower dose treatment groups. No related microscopic changes were observed in the thyroids of the affected animals. No differences were observed between the thyroids of male beagles in the treatment and control groups. No other differences in organ weights were observed between the treated and control animals.

No gross pathological differences were observed between beagles in the treatment and control groups. Male and female beagles in the 300/360 ppm treatment groups had slight vacuolated cell aggregations in lymphoid tissues (4/4 males, 2/4 females), slight to moderate inflammation of arteries in the epididymis (1/4 males) or cerebral meninges (1/4 females), and slight glandular cell vacuolation of the parathyroid (2/4 males). All microscopic tissue abnormalities, other than those mentioned, occurred randomly and sporadically in all study groups. No neoplastic tissue

was observed in beagles in the treatment or control groups.

The histologic changes at the highest dose in the 12-month study (8.22-8.46 mg/kg/day) closely resembled the histologic changes seen at the mid-dose (9.7-10.5 mg/kg/day) in a previous subchronic study with beagles (MRID 43444102) that was discussed by the chronic study author. A review of the 13-week subchronic study was provided to the Dynamac reviewers by OPPTS. It appeared that at this treatment level (approximately 8-10 mg/kg/day), increasing the dosing period from 13 weeks to 12 months did not intensify the severity of the lesions.

It was reported that the dogs in the 12-month study were examined by a Functional Observation Battery at 48-49 weeks and found normal (data not provided in this MRID). In the 13-week study, doses that were clearly toxic (45 mg/kg/day for 5.5 weeks followed by 33 mg/kg/day for 7.5 weeks in males, and 30 mg/kg/day for 13 weeks in females) resulted in death (1/4 males); marked weight loss (both sexes); decreased spontaneous motor activity (2 males); and vacuolation of nerve cells in the cervical spinal cord (4/4 males), the thoracic and lumbar spinal cords (2/4 males and 3/4 females), and the cerebellum and pons (1/4 females).

The LOEL is 8.22 mg/kg/day (300/360 ppm), based on increases in serum alanine aminotransferase, aspartate aminotransferase, and triglycerides levels, and the presence of tissue abnormalities, including vacuolated cell aggregations, arteritis, and glandular cell vacuolation (parathyroid). The NOEL is 2.68 mg/kg/day (100/120 ppm).

IV. Study deficiencies

No significant deficiencies were noted in this study.